

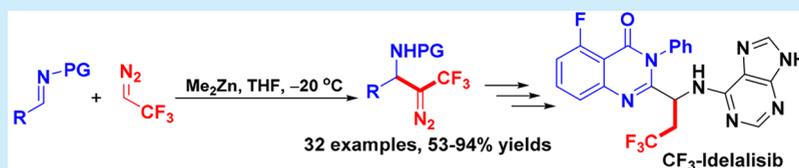
Zinc-Mediated Mannich-Type Reaction of 2,2,2-Trifluorodiazooethane with Imines: Access to β -CF₃-Amines

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S Supporting Information

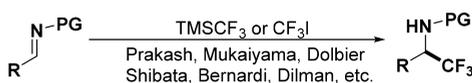


ABSTRACT: A zinc-mediated Mannich-type transformation of 2,2,2-trifluorodiazooethane with a series of imines has been described. This method provides facile access to a wide range of trifluorodiazooethyl-substituted amines in moderate to high yields under mild conditions. The synthetic utility of the afforded adducts is demonstrated by further transformations to valuable β -CF₃-amines.

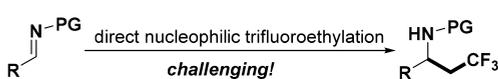
CF₃-containing amines represent a type of useful structural motif that has been frequently found in pharmaceuticals, agrochemicals, and bioorganic applications.¹ In the past two decades, great advances have been achieved in Mannich-type nucleophilic trifluoromethylation of imines, which has been recognized as a convergent and efficient manner to access α -CF₃ amines (Scheme 1a).² In sharp contrast, the analogous

Scheme 1. Preparation of α -CF₃-Amines and β -CF₃-Amines from Imines via Mannich-Type Reactions

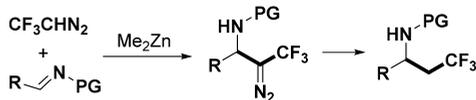
a) Trifluoromethylation of imines: *well developed*



b) Trifluoroethylation of imines: *unprecedented*



c) This work: trifluorodiazooethane as nucleophile

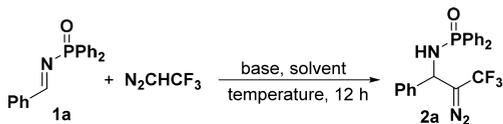


approach, named direct nucleophilic trifluoroethylation of imines to β -CF₃-amines, has not been reported, to the best of our knowledge (Scheme 1b).³ Indeed, this is a very challenging transformation owing to the difficult availability and poor stability of the trifluoroethyl nucleophiles.⁴ It has been demonstrated that trifluoroethyl nucleophiles such as α -trifluoromethyl carbanions and their corresponding organometallic species are prone to decompose because of their high

tendency of β -elimination with fluoride.⁵ One of the key factors that could increase the stability of the α -trifluoromethyl organometallic species is the degree of covalency in a bond between the carbon and metal.⁶ In this context, we envisioned that 2,2,2-trifluorodiazooethane (CF₃CHN₂),⁷ which has a diazo moiety as a potential stabilizing group, could serve as a suitable masked trifluoroethyl nucleophile after treatment with an organometallic base.⁸ To our delight, in the presence of dimethylzinc, a Mannich-type transformation of 2,2,2-trifluorodiazooethane with a series of imines smoothly underwent a reaction to afford trifluorodiazooethyl-substituted amines with moderate to high yields under mild conditions (Scheme 1c).⁹ After removal of the diazo moiety in the adducts, the expected β -CF₃-amines were generated in high yield, illustrating the successful development of CF₃CHN₂ as a masked trifluoroethyl nucleophile. Meanwhile, the diazo adducts could also be readily converted to trifluoromethyl ketal and alcohol by simple synthetic manipulations. Moreover, the preparation of the CF₃-containing analogue of the drug idelalisib has also been accomplished by using this protocol as a key step.¹⁰ Hence, as a part of our continued interest in the chemistry of trifluorodiazooethane,¹¹ herein, we report our results on this project.¹²

We started our investigation by choosing *N*-diphenylphosphinyl imine **1a** as the model substrate. Pleasingly, the target product **2a** was obtained in 88% yield when dimethylzinc was employed as the base in THF at -20 °C (Table 1, entry 1). Subsequently, several different organometallic bases (diethylzinc, *n*-butyllithium, and ethylmagnesium bromide) were evaluated, providing traces or much lower yields of desired

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Table 1. Optimization of Reaction Conditions^a

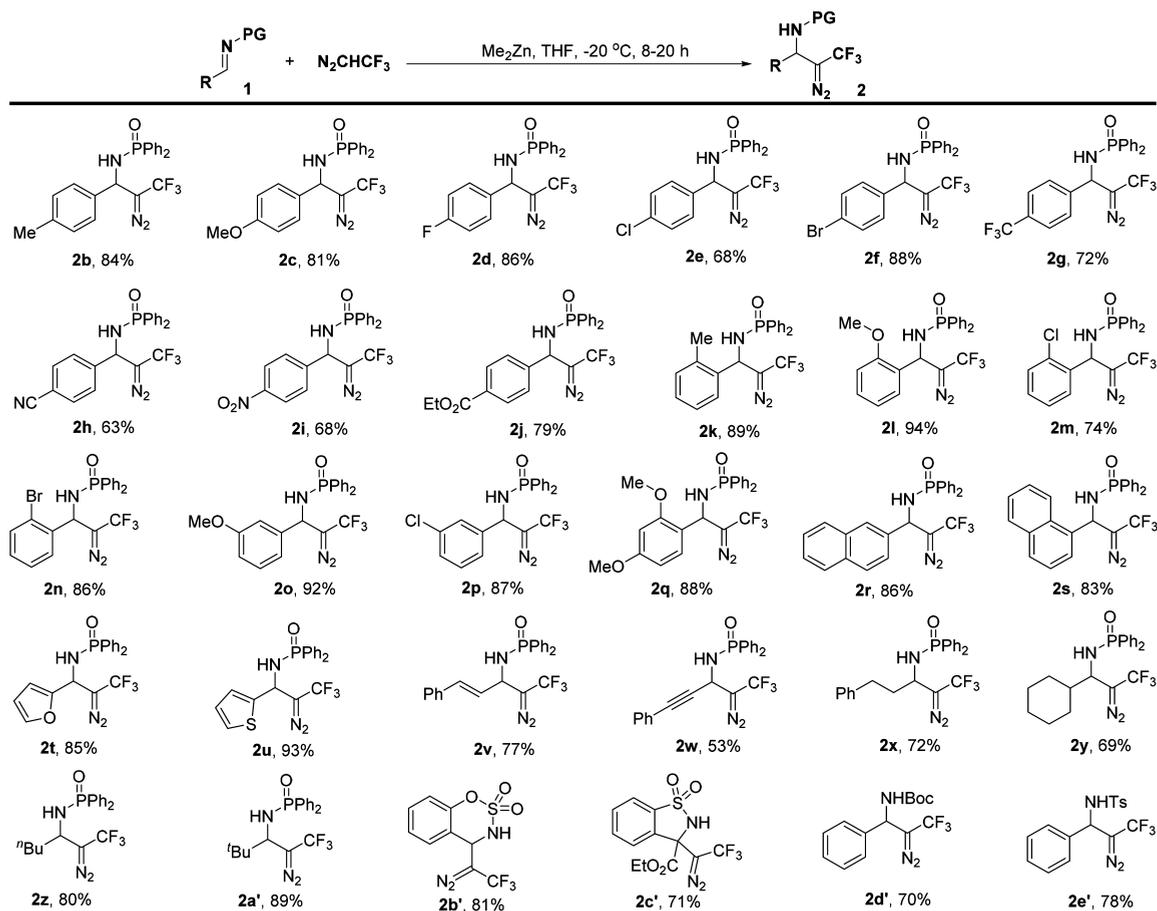
entry	solvent	base	temp (°C)	yield (%) ^b
1	THF	Me ₂ Zn	-20	88
2	THF	Et ₂ Zn	-20	68
3	THF	<i>n</i> -BuLi	-20	15
4	THF	EtMgBr	-20	trace
5	THF	Cs ₂ CO ₃	25	0
6	THF	DBU	25	0
7	CH ₃ CN	Me ₂ Zn	-20	78
8	DMF	Me ₂ Zn	-20	72
9	toluene	Me ₂ Zn	-20	0
10 ^c	THF	Me ₂ Zn	-20	73
11	THF	Me ₂ Zn	-10	63
12	THF	Me ₂ Zn	-30	80
13	THF	Me ₂ Zn	30	trace
14 ^d	THF	Me ₂ Zn	-20	81

^aGeneral reaction conditions: **1a** (0.5 mmol), CF₃CHN₂ (1.5 mmol), and base (1.0 mmol) in solvent (3 mL) at the given temperature for 12 h. ^bIsolated yield. ^cCF₃CHN₂ (1.0 mmol). ^d3 mmol scale of imine **1a**.

product **2a** (entries 2–4). Then, one inorganic base (Cs₂CO₃) and one organic base (DBU) were also examined in this

reaction, and no generation of **2a** was observed in both cases (entries 5 and 6).¹³ These results reveal that this transformation is very sensitive to the base used in the deprotonation step. Subsequently, a survey of different solvents was conducted, and we found that comparable yields were achieved in acetonitrile and DMF (entries 7–9). Finally, after a screen of other reaction parameters including temperature and reaction time (entries 10–13), the best reaction conditions of this Mannich-type transformation were established to be in THF at -20 °C for 12 h using dimethylzinc as the base (entry 1). Furthermore, gram-scale reaction was also conducted and smoothly produced **2a** in 81% yield (entry 14). In addition, control experiments with deuterium oxide were performed, and the deuterated trifluorodiazooethane was detected. These results suggest that the zinc reagent could be employed as a base to deprotonate the diazo substrate.¹⁴

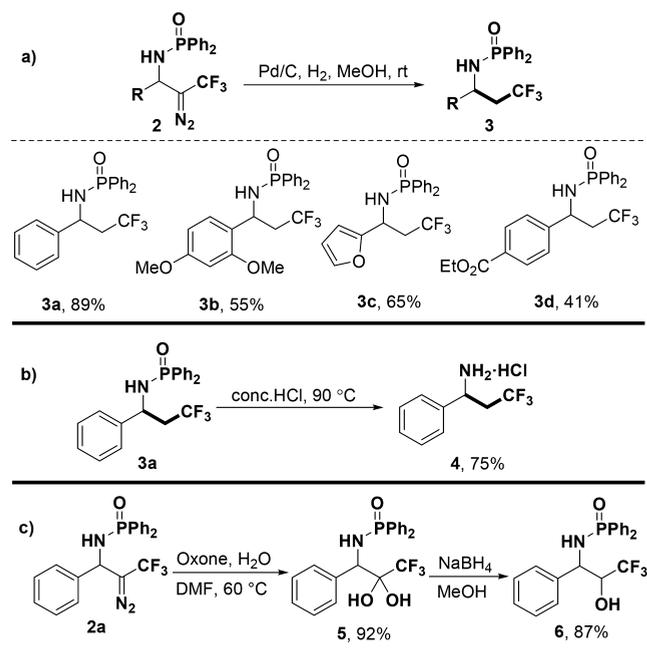
With the optimized reaction conditions in hand, we then set out to probe the substrate scope with a broad array of imines. These results are summarized in Scheme 2. For aromatic diphenylphosphinyl imines, regardless of the substituent's positions on the phenyl ring (*para*, *ortho*, and *meta*) or its electronic nature (electron-neutral, electron-donating, or electron-withdrawing), the desired trifluorodiazooethyl-substituted amines could be obtained smoothly in good to high yields (Scheme 2, products **2b–q**). 1-Naphthyl-, 2-naphthyl-, 2-furanyl-, and 2-thienyl-substituted imines were also found to be good substrates, thus generating the desired products **2r–u** in high yields. Remarkably, this method also tolerates

Scheme 2. Substrate Scope of Mannich-Type Reaction between CF₃CHN₂ and Imines

cinnamyl- and phenylethynyl-derived imines and led to the formation of **2v** and **2w**, albeit with slightly decreasing yields. It is worth noting that several alkyl-substituted imines, even those including the bulky *tert*-butyl substituent, are also compatible with this transformation, thus delivering corresponding adducts **2x–a'** in good to high yields. Moreover, two sulfonyl group protected cyclic imines also proved to be viable substrates and generated **2b'** and **2c'** in 81% and 71% yields, respectively. It should be noted that **2c'** was formed from a ketimine substrate, which further demonstrates the broad substrate scope of this transformation. In addition, both *tert*-butyloxycarbonyl (Boc)- and toluenesulfonyl (Ts)-derived imines have also been evaluated in this reaction. In these two cases, corresponding adducts **2d'** and **2e'** were obtained smoothly in 70% and 78% yields, respectively.

Subsequently, several synthetic elaborations of trifluorodiazoethyl-substituted amines have been implemented. As shown in [Scheme 3a](#), the diazo moiety of compound **2a** was removed

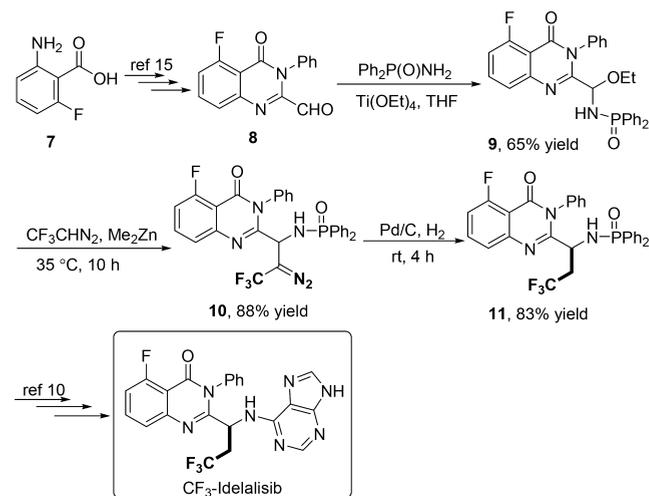
Scheme 3. Further Transformations of Mannich Adducts to β -CF₃ Amines



by treatment with Pd/C under a hydrogen atmosphere, thereby leading to the corresponding product **3a** in high yield. It is noteworthy that this compound is exactly the aforementioned nucleophilic trifluoroethylated product of imine, thus verifying the feasibility of our proposal. This transformation also tolerates substrates with an electron-donating group, electron-withdrawing group, and 2-furanyl group, thereby leading to the formation of compounds **3b–d** in decent yields. Also, the β -CF₃-amine **4** was obtained smoothly by a simple deprotection procedure ([Scheme 3b](#)). Next, trifluoromethyl ketal **5** was afforded with 92% yield when oxone was employed for the oxidation of **2a** ([Scheme 3c](#)). This compound could be readily converted into α -CF₃- β -amino alcohol **6** in high yield as a single diastereoisomer.¹⁵ This kind of β -amino alcohol holds promise for the preparation of peptidomimetics and other biologically active fluorinated compounds.¹⁶

To further demonstrate the synthetic utility of this method toward biologically active targets, we then became interested in the preparation of a β -CF₃-amine-containing drug analogue. Idelalisib, which is a drug used for the treatment of certain hematological malignancies, became our selection, as its CF₃-substituted analogue has been demonstrated to be a drug candidate for the treatment of diseases related to PI3K enzymes.¹⁰ As outlined in [Scheme 4](#), the imine precursor **9** was

Scheme 4. Preparation of CF₃-Containing Analogue of Drug Idelalisib



prepared in practical yield by condensation of diphenylphosphinamide with aldehyde **8** which was synthesized within 4 steps from 2-amino-5-fluorobenzoic acid **7** (see the [Supporting Information](#) for details).¹⁷ Subsequently, the Mannich-type reaction of **9** with CF₃CHN₂ was conducted smoothly to give the addition product **10** in 88% yield. Then, the target trifluoroethylated molecular **11** was obtained in 83% yield via an identical unmasked operation. This β -CF₃-amine compound holds promise for the downstream synthesis of CF₃-idelalisib according to the literature.¹⁰ The successful preparation of CF₃-idelalisib further demonstrates that our method can be employed as a complementary and expedient approach to access relevant targets bearing a β -CF₃-amino moiety.

In summary, we have developed a zinc-mediated Mannich-type reaction of CF₃CHN₂ to imines under mild conditions. This protocol provides efficient access to a wide range of trifluorodiazoethyl-substituted amines in moderate to high yields. Notably, the obtained adducts were readily converted to β -CF₃-amines, which shows the feasibility of utilizing CF₃CHN₂ as a masked nucleophilic trifluoroethylating reagent. Further studies, including an expansion of the substrate scope as well as an enantioselective version and mechanistic investigations, are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.8b02816](https://doi.org/10.1021/acs.orglett.8b02816).

Experimental details and spectral data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) For selected reviews, see: (a) Yoder, N. C.; Kumar, K. *Chem. Soc. Rev.* **2002**, *31*, 335. (b) Sani, M.; Volonterio, A.; Zanda, M. *ChemMedChem* **2007**, *2*, 1693. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (d) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (e) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (f) Huang, Y.-Y.; Yang, X.; Chen, Z.; Verpoort, F.; Shibata, N. *Chem. - Eur. J.* **2015**, *21*, 8664. (g) Li, S.; Ma, J.-A. *Chem. Soc. Rev.* **2015**, *44*, 7439.
- (2) For selected examples, see: (a) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589. (b) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538. (c) Kawano, Y.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 894. (d) Xu, W.; Dolbier, W. R. *J. Org. Chem.* **2005**, *70*, 4741. (e) Levin, V. V.; Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Eur. J. Org. Chem.* **2008**, *2008*, 5226. (f) Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6324. (g) Radchenko, D. S.; Michurin, O. M.; Chernykh, A. V.; Lukin, O.; Mykhailiuk, P. K. *Tetrahedron Lett.* **2013**, *54*, 1897.
- (3) Uneyama, K.; Yamazaki, T. *J. Fluorine Chem.* **2017**, *203*, 3.
- (4) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817.
- (5) (a) Zhao, C.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1033. (b) Han, J.-B.; Hao, J.-H.; Zhang, C.-P.; Qin, H.-L. *Curr. Org. Chem.* **2015**, *19*, 1554. (c) Tóth, B. L.; Kovács, S.; Sályi, G.; Novák, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 1988. (d) Maraswami, M.; Pankajakshan, S.; Chen, G.; Loh, T.-P. *Org. Lett.* **2017**, *19*, 4223. (e) Kovács, S.; Tóth, B. L.; Borsik, G.; Bihari, T.; May, N. V.; Stirling, A.; Novák, Z. *Adv. Synth. Catal.* **2017**, *359*, 527.
- (6) (a) Jiang, B.; Xu, Y. *J. Org. Chem.* **1991**, *56*, 7336. (b) Watanabe, H.; Yamashita, F.; Uneyama, K. *Tetrahedron Lett.* **1993**, *34*, 1941. (c) Watanabe, H.; Yan, F.-Y.; Sakai, T.; Uneyama, K. *J. Org. Chem.* **1994**, *59*, 758.
- (7) For reviews, see: (a) Grygorenko, O. O.; Artamonov, O. S.; Komarov, I. V.; Mykhailiuk, P. K. *Tetrahedron* **2011**, *67*, 803. (b) Qiu, D.; Qiu, M.; Ma, R.; Zhang, Y.; Wang, J. *Huaxue Xuebao* **2016**, *74*, 472. (c) Mertens, L.; Koenigs, R. M. *Org. Biomol. Chem.* **2016**, *14*, 10547. For recent selected examples, see: (d) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938. (e) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9085. (f) Argintaru, O. A.; Ryu, D.; Aron, I.; Molander, G. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 13656. (g) Mykhailiuk, P. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 6558. (h) Luo, H. Q.; Wu, G. J.; Zhang, Y.; Wang, J. B. *Angew. Chem., Int. Ed.* **2015**, *54*, 14503. (i) Arkhipov, A. V.; Arkhipov, V. V.; Cossy, J.; Kovtunen, V. O.; Mykhailiuk, P. K. *Org. Lett.* **2016**, *18*, 3406. (j) Hock, K. J.; Mertens, L.; Koenigs, R. M. *Chem. Commun.* **2016**, *52*, 13783. (k) Hyde, S.; Veliks, J.; Liegault, B.; Grassi, D.; Taillefer, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2016**, *55*, 3785. (l) Hock, K. J.; Mertens, L.; Metzke, F. K.; Schmittmann, C.; Koenigs, R. M. *Green Chem.* **2017**, *19*, 905. (m) Peng, S.-Q.; Zhang, X.-W.; Zhang, L.; Hu, X.-G. *Org. Lett.* **2017**, *19*, 5689. (n) Britton, J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2017**, *56*, 8823. (o) Bu, X.-B.; Wang, Z.; Wang, X.-D.; Meng, X.-H.; Zhao, Y.-L. *Adv. Synth. Catal.* **2018**, *360*, 2945. (8) Qin, S.; Zheng, Y.; Zhang, F.-G.; Ma, J.-A. *Org. Lett.* **2017**, *19*, 3406.
- (9) For reviews, see: (a) Zhao, Y.; Wang, J. *Synlett* **2005**, *2005* (19), 2886. (b) Zhang, Y.; Wang, J. *Chem. Commun.* **2009**, 5350. For selected examples of Mannich-type reaction of diazo reagent to imines, see: (c) Zhao, Y.; Ma, Z.; Zhang, X.; Zou, Y.; Jin, X.; Wang, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5977. (d) Uruguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360. (e) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. (f) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011**, *3*, 642. (g) Hashimoto, T.; Kimura, H.; Nakatsu, H.; Maruoka, K. *J. Org. Chem.* **2011**, *76*, 6030. (h) Zhang, H.; Wen, X.; Gan, L.; Peng, Y. *Org. Lett.* **2012**, *14*, 2126. (i) Wen, X.; Chen, J.; Peng, Y. *Adv. Synth. Catal.* **2014**, *356*, 3794. (j) Chen, J.; Wen, X.; Wang, Y.; Du, F.; Cai, L.; Peng, Y. *Org. Lett.* **2016**, *18*, 4336. (k) Unhale, R. A.; Sadhu, M. M.; Ray, S. K.; Biswas, R. G.; Singh, V. K. *Chem. Commun.* **2018**, *54*, 3516. (10) (a) Askew, B. C.; Furuya, T. U.S. Patent 20140296260A1, 2014. (b) Xi, N.; Wang, L.; Wu, Z.; Feng, X.; Wu, Y. U.S. Patent 9518046B2, 2016. (c) Askew, B. C.; Furuya, T. U.S. Patent 20160067249A1, 2016. (11) (a) Li, F.; Nie, J.; Sun, L.; Zheng, Y.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6255. (b) Zhang, F.-G.; Wei, Y.; Yi, Y.-P.; Nie, J.; Ma, J.-A. *Org. Lett.* **2014**, *16*, 3122. (c) Zhu, C. L.; Yang, L. J.; Li, S.; Zheng, Y.; Ma, J.-A. *Org. Lett.* **2015**, *17*, 3442. (d) Guo, R.; Zheng, Y.; Ma, J.-A. *Org. Lett.* **2016**, *18*, 4170. (e) Chen, Z.; Zheng, Y.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2017**, *56*, 4569. (f) Zhang, F.-G.; Zeng, J.-L.; Tian, Y.-Q.; Zheng, Y.; Cahard, D.; Ma, J.-A. *Chem. - Eur. J.* **2018**, *24*, 7749. (g) Zhang, F.-G.; Lv, N.; Zheng, Y.; Ma, J.-A. *Chin. J. Chem.* **2018**, *36*, 723. (12) It should be mentioned that in the presence of BF₃·Et₂O or chiral phosphoric acid, the reaction of CF₃CHN₂ with imines would generate CF₃-substituted aziridines as reported by Carreira and Cahard: (a) Künzi, S. A.; Morandi, B.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 1900. (b) Chai, Z.; Bouillon, J. P.; Cahard, D. *Chem. Commun.* **2012**, *48*, 9471. (13) Pieber, B.; Kappe, C. O. *Org. Lett.* **2016**, *18*, 1076. (14) See the [Supporting Information](#) for more details and a proposed mechanistic pathway. (15) The high stereoselectivity observed in the reduction process can be rationalized by the Newman projection, which has already been discussed in previous reports: Zhao, Y.; Jiang, N.; Chen, S.; Peng, C.; Zhang, X.; Zou, Y.; Zhang, S.; Wang, J. *Tetrahedron* **2005**, *61*, 6546. As well as refs [9c](#), [d](#), and [h](#). (16) Mlostoń, G.; Obijalska, E.; Heimgartner, H. *J. Fluorine Chem.* **2010**, *131*, 829. (17) (a) Chenard, B. L.; Welch, W. M.; Blake, J. F.; Butler, T. W.; Reinhold, A.; Ewing, F. E.; Menniti, F. S.; Pagnozzi, M. J. *J. Med. Chem.* **2001**, *44*, 1710. (b) Wahl, B.; Cabré, A.; Woodward, S.; Lewis, W. *Tetrahedron Lett.* **2014**, *55*, 5829. (c) Kumar, D.; Jadhavar, P. S.; Nautiyal, M.; Sharma, H.; Meena, P. K.; Adane, L.; Pancholia, S.; Chakraborti, A. K. *RSC Adv.* **2015**, *5*, 30819. (d) Yang, Y.; Yu, Y.; Li, X.; Li, J.; Wu, Y.; Yu, J.; Ge, J.; Huang, Z.; Jiang, L.; Rao, Y.; Yang, M. *J. Med. Chem.* **2017**, *60*, 1994.